527 Rec'd PCT/PTO 31 OCT 2000

(FORM PTO-1390 (REV 10-2000)) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	US APPLICATION NO. (If known, see 37 CFR 1.5)
1700 F US	09/674403

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US99/10179	10.05.99 (10 May 1999)	19.05.98 (19 May 1998)

TITLE OF INVENTION: SEROTONERGIC 5HT7 RECEPTOR COMPOUNDS FOR TREATING OCULAR AND CNS DISORDERS

APPLICANT(S) FOR DO/EO/US: Jesse A. May, Thomas R. Dean, Najam A. Sharif, and Hwang-Hsing Chen

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☑ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☑ This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. ☐ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☑ has been communicated by the International Bureau.
   c. ☑ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. ☑ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☑ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☑ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

SCANNED, #

Items 11 to 16 below concern document(s) or information included:

11. ☑ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☑ Other items or information:

COPY of Recorded Assignment
COPY International Search Report
COPY International Preliminary Examination Report

Express Mail No.
EK810444575US

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/674403	PCT/US99/10179	1700 F US

529 Rec'd PCT/PTO 31 OCT 2000

17. ☑ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	

ENTER APPROPRIATE BASIC FEE AMOUNT =				$ 710.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	49 - 20 =	29	X **$18.00**	$ 522.00	
Independent claims	44 - 3 =	41	X **$80.00**	$ 3,280.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$ 4,512.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$	
SUBTOTAL =				$ 4,512.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 4,512.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ .00	
TOTAL FEES ENCLOSED =				$	
				Amount to be refunded:	$
				charged:	$

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☑ Please charge my Deposit Account No. 01-0682 in the amount of $ 4,512.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 01-0682. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

26356
PATENT ,TRADEMARK OFFICE

Sally Yeager
SIGNATURE

Sally Yeager
(817) 551-4031
NAME

32,757
REGISTRATION NUMBER

SEROTONERGIC 5HT$_7$ RECEPTOR COMPOUNDS FOR TREATING OCULAR AND CNS DISORDERS

The present invention is directed to the use of compounds with serotonergic 5HT$_7$ receptor affinity (Compound) (some of which are novel), to improve blood flow to the optic nerve head and the retina, provide neuroprotection, lower intraocular pressure (IOP), and treat retinal diseases, such as, glaucoma, age related macular degeneration (ARMD), optic neuritis, ischemic disorders, diabetic retinopathy, and retinal edema. The Compounds are also useful for treating sleep disorders, depression, and other psychiatric disorders, such as, schizophrenia, anxiety, obsessive compulsive disorder, circadian rhythm disorders, and centrally and peripherally mediated hypertension.

Background of the Invention

Serotonin (5-hydroxy tryptamine; 5HT) is an endogenous biogenic amine with a well defined neurotransmitter function in many tissues of the body including the eye [Zifa and Fillion, *Pharmacol. Rev.*, 44:401-458, 1992; Hoyer et al., *Pharmacol. Rev.*, 46:157-203, 1994; Tobin et al., *J. Neurosci.*, 8:3713-3721, 1988].

5HT can interact with at least seven major 5HT receptors (5HT$_1$ - 5HT$_7$) and additional subtypes within these families to initiate intracellular biochemical events such as stimulation of second messengers (e.g. cAMP, inositol trisphosphate) eventually leading to the final biological response, for example, tissue contraction or hormone release, etc. [Hoyer et al., *supra*; Martin et al., *Trends Pharmacol. Sci.*, 19:2-4, 1998]. Receptor subtypes within the 5HT$_1$ family are negatively coupled to adenylyl cyclase (AC) and cause inhibition of cAMP production, while 5HT$_4$, 5HT$_6$, and 5HT$_7$ receptors are positively coupled to AC and thus stimulate cAMP production when activated by 5HT [Martin et al., *supra*]. The receptors in the 5HT$_2$ family are positively coupled to phospholipase C (PLC) and thus generate inositol phosphates and mobilize intracellular calcium when activated to mediate the effects of 5HT. The 5HT$_3$ receptor is unique in that it couples to an ion channel which gates sodium, potassium, and calcium [Hoyer et al., *supra*].

The human and animal $5HT_7$ receptor has only recently been cloned, expressed, and shown to be present in various brain areas and peripheral tissues [Eglen et al., *Trend Pharmacol. Sci.*, 18:104-107, 1997]. Recent studies have shown there to be four splice variants of the $5HT_7$ receptor [Heidmann et al., *J. Neurochem.*, 68:1372-1381, 1997]. It has been proposed that the $5HT_7$ receptor may be involved in the pathophysiology of sleep disorders, depression, and other psychiatric disorders [Eglen et al., *supra*]. In the periphery, stimulation of $5HT_7$ receptors results in relaxation of blood vessels and hence vasodilation [Eglen et al., *supra*]. Improving blood flow to the back of the eye, including the retina, the macula, and the optic nerve head is believed to be beneficial in the treatment of a number of retinal diseases, for example, glaucoma, ARMD, and diabetic retinopathy [Chiou, et al., *J. Ocular Pharmacol.* 9:13-24 (1993)].

Serotonergic nerves innervate the eye [Tobin et al., *J. Neurosci.*, 8:3713-3721, 1988] and 5HT has been found in the aqueous humor of human eyes [Martin et al., *Ophthalmol.*, 95:1221-1226, 1988]. In addition, receptor binding sites for [^{3}H]5HT have been demonstrated and pharmacologically characterized in the iris-ciliary body (ICB) of rabbits [Mallorga and Sugrue, *Curr. Eye Res.*, 6:527-532, 1987 and Chidlow et al., *Invest. Ophthalmol. Vis. Sci.*, 36:2238-2245, 1995]. These 5HT binding sites have been shown to be functionally coupled to second messenger generation in rabbits [Tobin and Osborne, *J. Neurochem.*, 53:686-601, 1989 and Tobin et al., *J. Neurosci, supra*]. In the human ICB these binding sites are characterized as $5HT_{1A}$ and $5HT_2$ receptors [Barnet and Osborne, *Exp. Eye Res.*, 57:209-216, 1993]. In addition, the presence of mRNAs for $5HT_{1a}$ and $5HT_7$ receptors in the rabbit ICB have been reported [Chidlow et al., *Invest. Ophthalmol. Vis. Sci., supra* and Osborne and Chidlow, *Ophthalmologica*, 210:308-314, 1996]. The precise functions of these receptors in the eye are unknown, especially the $5HT_7$ subtype(s).

5HT or 5-carboxamidotryptamine (5-CT) topically applied to the rabbit eye raise intraocular pressure in the anterior chamber of the eye [Meyer-Bothling et al., *Invest. Ophthalmol. Vis. Sci.*, 34:3035-3042, 1993]. By contrast, it has been shown that topically applied 5HT lowers IOP [Krootila et al., *J. Ocular Pharmacol.*, 3:279-290, 1987 (intracamerally 5HT raised IOP and caused breakdown of the blood-aqueous barrier)]. In addition, the 5HT uptake inhibitor, fluoxetine (Prozac®), also raises IOP in human subjects

upon oral administration [Costagliola et al., *Br. J. Ophthalmol.*, 80:678, 1996] and may cause glaucoma [Ahmad, *Ann. Pharmacother.*, 25:436, 1992]. However, the 5HT receptor subtype(s) involved in the IOP-elevating effects of 5HT, 5-CT and fluoxetine are unknown.

Studies conducted in rabbits with 8-hydroxy DPAT and MKC-242 ($5HT_{1A}$ agonists) have shown these compounds lower IOP [Osborne and Chidlow, *Ophthalmologica*, 210:308-319, 1996, and EP 0771563-A2]. In addition, 5-methylurapidil ($5HT_{1A}$ agonist) lowered IOP in glaucomatous monkeys [Wang, et al., *Curr. Eye Res.*, 16:679-775, 1997]. Both MKC-242 and 5-methylurapidil are relatively potent $\alpha 1$ receptor antagonists ($\alpha 1$ antagonists are known to lower IOP in rabbits, monkeys, and man). The mechanism of action for lowering IOP by 5-methylurapidil has been attributed to its $\alpha 1$ antagonist activity and not its $5HT_{1A}$ agonist activity [Wang, et al., *Invest. Ophthal. Vis. Sci.*, 39(Suppl):2236-488, 1998]. U.S. Patent No. 5,693,654, discloses $5HT_1$ receptor agonists for lowering IOP. WO92/20333 discloses certain $5HT_{1A}$ agonists for the treatment of glaucoma.

Methysergide ($5HT_2$ antagonist) lowered IOP in rabbits [Krootila, et al., *Esp. Eye Res., supra*]. Ketanserin ($5HT_{2A/C}$ antagonist), also with significant $\alpha 1$ antagonist activity, lowers IOP in rabbits and man [Chan, et al., *J. Ocular Pharmacol.*, 1:137-147, 1985 and Costagliola, et al., *Ex. Eye Res.*, 52:507-510, 1991]. Saprogrelate ($5HT_{2A}$ antagonist) lowers IOP in rabbits and in man when dosed topically or orally [Mano, et al., *Invest. Ophthal. Vis. Sci.*, 36(Suppl):3322-309, 1995, and Takenaka, et al., *Invest Ophthal. Vis. Sci.*, 36(Suppl):3390-377, 1995]. EP 522226 and U.S. Patent No. 5,290,781 disclose the use of ketanserin and its derivatives for treating ocular hypertension. U.S. Patent Nos. 5,290,781 and 5,106,555 discloses the use of certain $5HT_2$ antagonists for lowering IOP. U.S. Patent No. 5,652,272 discloses saprogrelate for reducing IOP. U.S. Patent No. 5,538,974 discloses opthalmic compositions of certain $5HT_2$ antagonists for lowering IOP.

U.S. Patent No. 5,011,846 discloses certain $5HT_3$ receptor antagonists for treating glaucoma.

WO 97/17345 discloses that particular compounds with $5HT_4$ serotonergic receptor agonist or antagonist activity are useful for treating psychiatric, gastrointestinal, lower urinary, and cardiovascular disorders. The publication mentions the compounds may also be useful for glaucoma.

As evidenced by the previous discussion, it is not clear which serotonergic receptor activity is responsible for lowering IOP. Moreover, a number of these compounds are known to have activity at other receptors which are known to be involved in lowering IOP. Furthermore, it has not been cleared which receptor(s) might be responsible for increasing blood flow and providing neuroprotection in the eye.

Summary of the Invention

The present invention is directed to Compounds, some of which are novel, that have $5HT_7$ receptor affinity, and the use of compounds with $5HT_7$ receptor affinity to lower IOP, improve blood flow to the optic nerve head and the retina, provide neuroprotection, and control damage associated with diseases, such as, glaucoma, ARMD, optic neuritis, ischemic disorders, and retinal edema by functioning as neuroprotectants. Compositions of the compounds are contemplated for such uses. The Compounds are also useful for treating sleep disorders, depression, and other psychiatric disorders, such as, schizophrenia, anxiety, obsessive compulsive disorder, circadian rhythm disorders, and centrally and peripherally mediated hypertension.

Detailed Description Preferred Embodiments

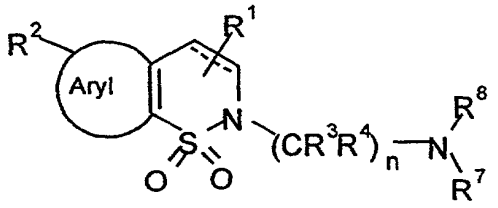
It has been unexpectedly discovered that $5HT_7$ receptors are present in the retina, choroid, and possibly the optic nerve head. Furthermore, sertonergic Compounds which possess a relatively high affinity (K_i = 0.01 - 200nM) for $5HT_7$ receptors effectively lower elevated IOP. It is believed that these Compounds can improve blood flow, and provide neuroprotection to the optic nerve head and the retina. The Compounds' (preferrably Compounds that are agonists or partial agonists) ability to improve blood flow to the optic nerve head and the retina and other characteristics are believed to render them

neuroprotective. The novel Compounds disclosed herein are also useful for treating sleep disorders, depression, and other psychiatric disorders.

Compounds found in the following applications are useful according to the present invention and are incorporated herein by reference: EP 738513-A1; WO 97/29097; WO 97/48681; WO 97/49695; and WO 98/00400. Specific Compounds include: LY-215840, SB-258719, and DR-4004.

The following novel Compounds and their pharmaceutically acceptable salts and solvates are useful for treating persons with the diseases and disorders previously described.

Formula I



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

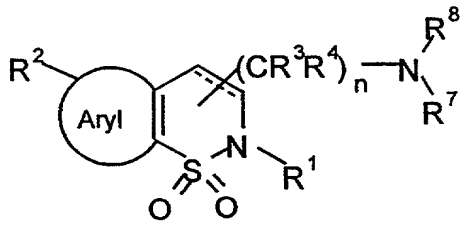
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine

or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2.

Formula II



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2 NR^5R^6$; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2 NR^5R^6$; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2 NR^5R^6$, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6

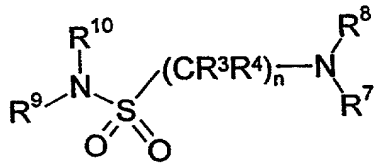
membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2.

Formula III



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

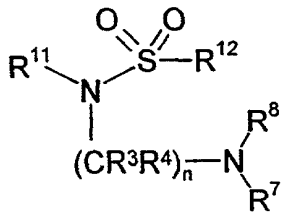
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4.

Formula IV



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

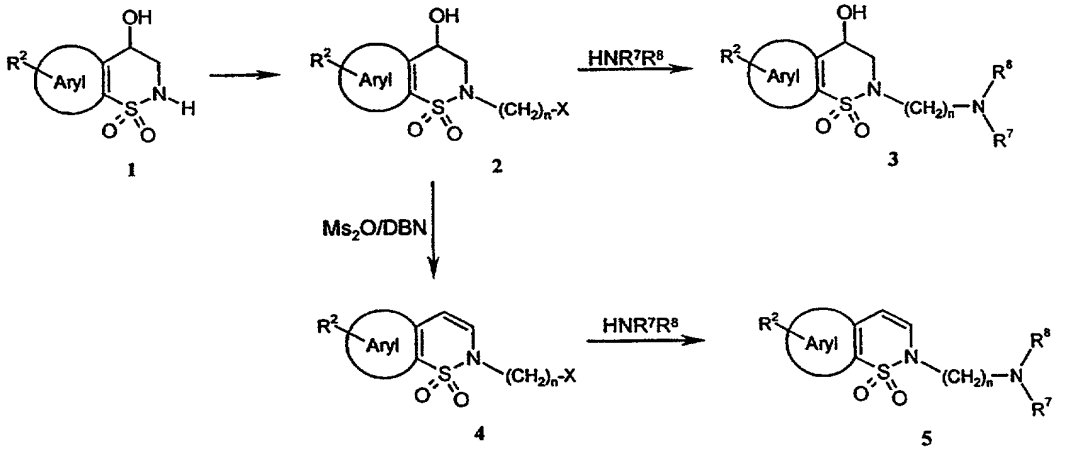
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4.

The compounds of the present invention can be prepared using chemical synthesis procedures herein described. The preferred method for preparing compounds of Formula I is illustrated in Scheme I. For example, the thiazine alcohols **1**, which can be prepared by methods described in U.S.Patents 5,344,929 and 5,470,973, or in *J. Org. Chem.* **31**, 162 (1966), can be selectively alkylated on the nitrogen atom at position two with, for example, a dihaloalkane using procedures known to the art to give **2**, where X is a halogen atom such as chlorine, bromine, or iodine. Compounds **2** can be treated with amines by known procedures to provide compounds of Formula I (**3**) where R^1 is hydroxyl, further these alcohols **3** can be treated with an alkylhalide to effect alkylation on oxygen to provide the ethers, R^1 is alkoxy. Alternately, **2** can be dehydrated by using methods described in U.S. Patent 5,538,966 to give compounds **4** which can be further reacted with amines to give compounds of Formula I where R^1 is hydrogen and the thiazine ring contains a double bond (**5**).

Scheme I

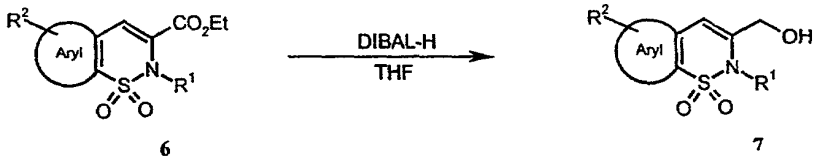


Procedures for preparing compounds of Formula II are illustrated in Scheme II. For example, the 3-hydroxymethyl thiazine compounds **7** can be prepared from the esters **6** by methods described in U.S. Patent 5,538,966 [Equation (a)]. Further, compounds **7** can be aminated using a variety of well known procedures, such as initial activation of the hydroxyl group by forming a sulfonate ester, followed by reaction of this intermediate with the desired primary or secondary amine to give compounds **8** of Formula II where R^3 and R^4 are hydrogen and n is 1 [Equation (b)]. Additionally, using **7** as an intermediate with which to initiate a suitable

homologation sequence, compounds of Formula II wherein R^3 and R^4 are hydrogen and n is 2 or 3 can be prepared; an example of such a homologation sequence employing 7 is illustrated in Equations (c) and (d), respectively.

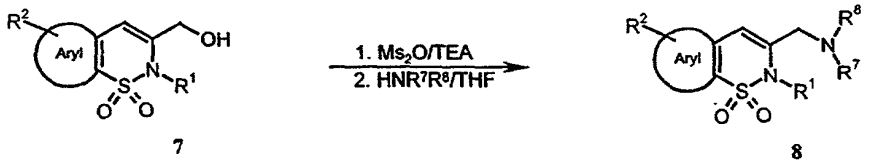
Scheme II

(a)



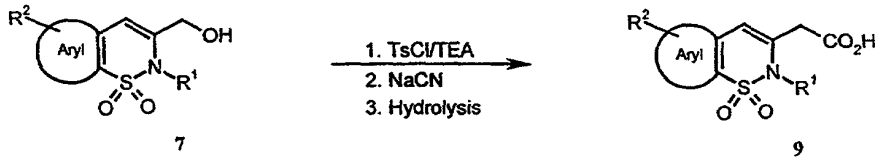
6 7

(b)

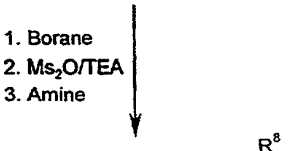


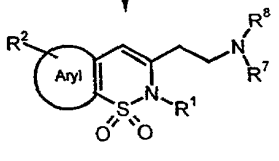
7 8

(c)



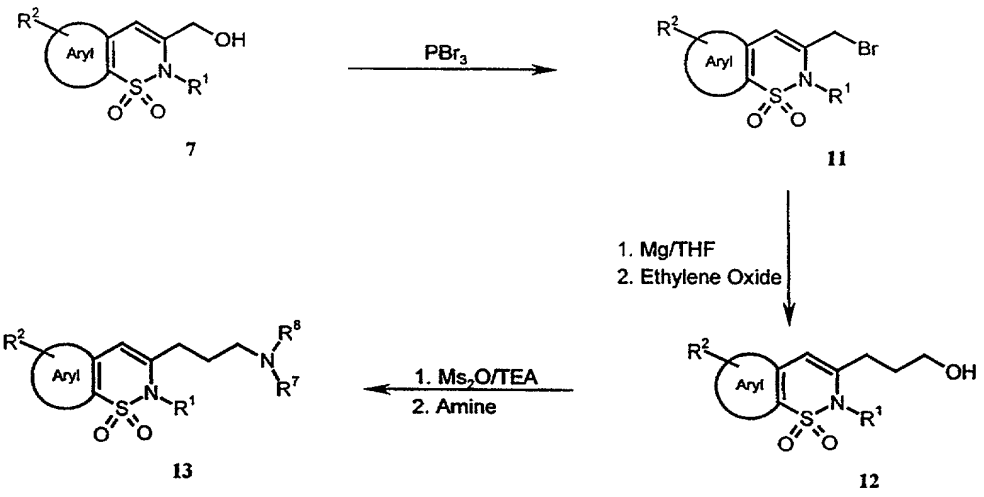
7 9





10

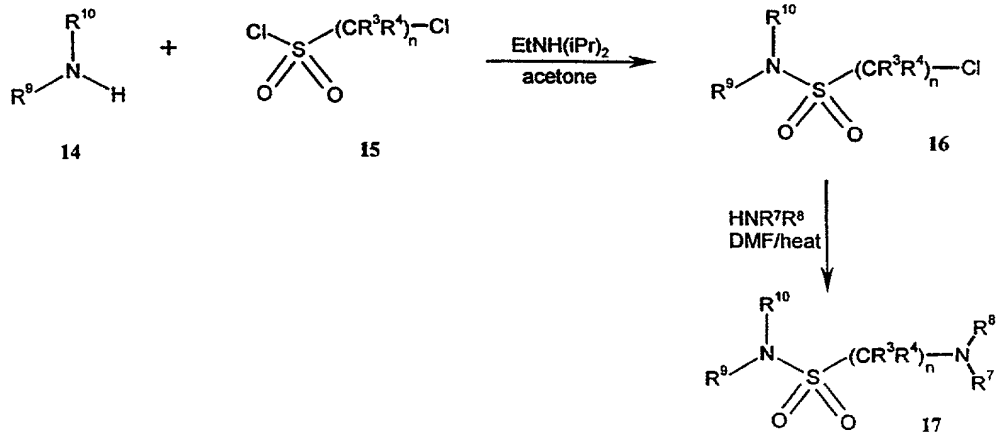
(d)



7 11 12 13

The preparation of compounds of Formula III can be readily accomplished by procedures herein described. For example, reaction of the desired amine **14** with the appropriate haloalkylsulfonyl chloride **15** in an inert solvent in the presence of a suitable base [see e.g., *J. Med. Chem.* **40**, 3217 (1997)] to give the haloalkylsulfonamide intermediate **16**. Subsequent reaction of **16** with the appropriate primary or secondary amine employing known procedures, provides compounds **17** of Formula III.

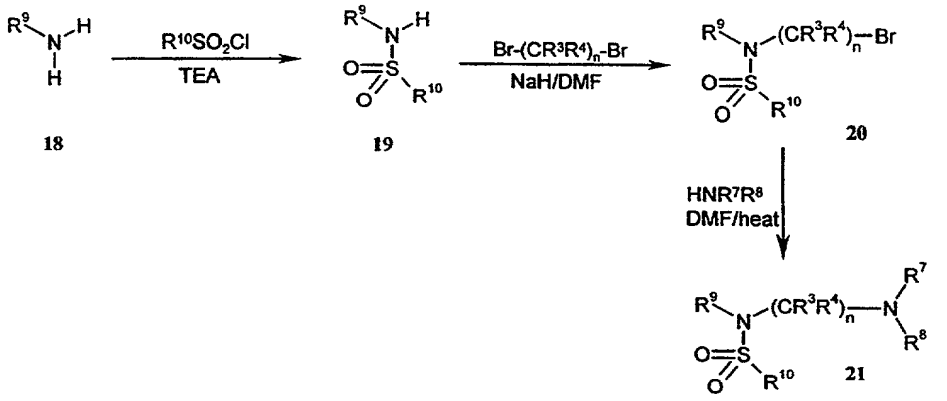
Scheme III



14 15 16 17

The preparation of compounds of Formula IV can be readily accomplished by procedures herein described. For example, reaction of the desired primary amine **18** with the appropriate sulfonyl chloride in an inert solvent in the presence of a suitable base provides the intermediate secondary sulfonamide **19** which can be alkylated by known procedures with the appropriately substituted alkyldibromide to give the haloalkylsulfonamide intermediate **20**. Subsequent reaction of **20** with the appropriate primary or secondary amine employing well known procedures provides compounds **21** of Formula IV.

Scheme IV



It is evident that some of the Compounds of Formula I - IV will include asymmetric atoms, all enantiomers and diastereomers are contemplated.

The term heteroaromatic ring refers to thiophene, furan, pyrrole, pyridine, pyrimidine, pyridazine and pyrazine.

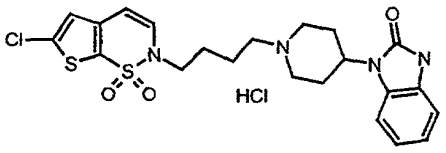
The Compounds can be administered systemically or locally to the eye (e.g., topically, intracamerally, or via an implant). The Compounds are preferrably incorporated into topical ophthalmic formulations for delivery to the eye. The Compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic

suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a Compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the Compound. Furthermore, the ophthalmic solution may contain an agent to increase viscosity, such as, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-940, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated. The Compounds can be formulated for systemic (e.g. oral, I.V., I.M., subcutaneous) delivery according to methods known to one skilled in the art. For systemic delivery the Compounds are delivered at concentrations of 0.005 - 1000 mg. per dose, preferrably 0.05 - 20.0, most preferrably 0.2 - 5 mg. per dose. The Compounds will be dosed 1-4 times per day according to the discretion of a skilled clinician.

For ophthalmic medications the Compounds are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The Compounds will normally be contained in these formulations in an amount .01% to 5% by weight, but preferably in an amount of .25% to 2% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the routine discretion of a skilled clinician. The preferred Compounds are those set forth in Examples 1, 1.1, 1.2, 1.6, 1.8, 2.3, 2.7, 2.10, 2.1, 2.4, 3, 3.1, 3.11, 3.5, and 3.10.

Example 1

6-Chloro-2-[4-[4-(2*H*-benzimidazo-2-oxo-1-yl)piperidin-1-yl]butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide Hydrochloride



Step 1. A solution 6-chloro-3,4-dihydro-2*H*-thieno[3,2-*e*]-1,2-thiazine-4-ol 1,1-dioxide (9.0 g, 37.6 mmol) in dimethylformamide (200 mL, anhydrous) and sodium hydride (60% in oil, 1.66 g, 41.5 mmol) was reacted with 1,4-dibromobutane at 0°. The reaction was stirred in an ice bath for 30 min and then it was allowed to warm to room temperature and stir for three days. The mixture was poured into ice water (400 mL) and extracted with diethyl ether (2 x 200 mL). The combined organic layers were washed with water (200 mL), brine (200 mL) and then were dried over magnesium sulfate and evaporated. The resulting residue was purified by silica gel flash chromatography with hexane/ethyl acetate (7:3) to give 6-chloro-3,4-dihydro-2-(4-bromobutyl)-2*H*-thieno[3,2-*e*]-1,2-thiazine-4-ol 1,1-dioxide as a colorless oil (10.62 g, 75%); the ^{1}H NMR was consistent with the structure.

Step 2. The product from Step 1 (10.6 g, 28.3 mmol) was dissolved in tetrahydrofuran (anhydrous, 400 mL) and treated with triethyl amine (9.88 mL, 70.9 mmol) and methane sulfonic anhydride (9.86 g, 56.6 mmol) at room temperature and stirred for one hour. The suspension was concentrated and taken up in dimethylformamide (anhydrous, 120 mL). This mixture was heated at 160° for 45 min. The reaction mixture was poured into ice water (300 ml) and extracted with dichloromethane (300 mL). The organic layer was washed with water (2 x 200 mL), dried over magnesium sulfate and evaporated to a brown oil. After silica flash chromatography with hexane/ethyl acetate 6-chloro-2-(4-bromobutyl)-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide was obtained as a yellow oil (4.97 g, 49%); the ^{1}H NMR. was consistent with the structure.

Step 3. A solution of 4-(2*H*-benzimidazo-2-oxo-1-yl)piperidine (0.30 mmol) in DMF (1.6 mL, anhydrous) and triethyl amine (0.5 mL) was treated with the product of Step 2 (0.103 g,

0.29 mmol) and stirred at 70° for 20 hours and then at room temperature for two days. The reaction mixture was diluted with ethyl acetate (3 mL) and water (4 mL). Saturated sodium bicarbonate (1 mL) was added and the layers were mixed followed by removal of the aqueous layer. The organic layer was washed with water (6 mL) and evaporated to give a residue that was dissolved in ethanol and treated with 1 N hydrochloric acid in ether. After evaporation the desired product was obtained as a white solid (69.2 mg, 45%): ^{1}H NMR and MS (M + H 493) were consistent with the structure.

By following the procedures of Example 1, but replacing 4-(2*H*-benzimidazo-2-oxo-1-yl)piperidine in Step 3 with the appropriate amine, the following compounds were prepared. The ^{1}H NMR spectrum and the mass spectrum for each of these compounds were consistent with the assigned structure.

1. 6-Chloro-2-[4-(4-phenylpiperazin-1-yl)butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride;
2. 6-Chloro-2-[4-[4-(2-fluorophenyl)piperazin-1-yl]butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride;
3. 6-Chloro-2-[4-[4-hydroxy-4-(4-chlorophenyl)piperidin-1-yl]butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride;
4. 6-Chloro-2-[4-[4-hydroxypiperidin-1-yl]butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride.

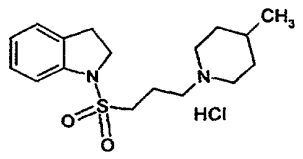
By following the procedures of Example 1, but replacing the 1,4-dibromobutane in Step 1 with 1,3-dibromopentane and 4-(2*H*-benzimidazo-2-oxo-1-yl)piperidine in Step 3 with the appropriate amine, the following compounds were prepared. The ^{1}H NMR spectrum and the mass spectrum for each of these compounds were consistent with the assigned structure.

5. 6-Chloro-2-[3-[4-phenylpiperazin-1-yl]propyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride;
6. 6-Chloro-2-[3-[4-(3-trifluoromethylphenyl)piperazin-1-yl]propyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride;

7. 6-Chloro-2-[3-[4-(2-fluorophenyl)piperazin-1-yl]propyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride;
8. 6-Chloro-2-[3-[4-(2*H*-benzimidazol-2-oxo)piperidin-1-yl]propyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide hydrochloride.

Example 2

3-(4-Methylpiperidin-1-yl)propylsulfonyl-2,3-dihydro-1*H*-indole Hydrochloride



Step 1. To a solution of indoline (4.00 g, 33.6 mmol) in 100 mL of acetone at 0°C was added 3-chloropropanesulfonyl chloride (5.95 g, 33.6 mmol) with stirring. A solid precipitated from the solution. Diisopropylethylamine (4.33 g, 33.6 mmol) was added in two portions and the reaction mixture became a homogenous solution. The mixture was stirred for 30 min, warmed to ambient temperature, and evaporated to dryness. The crude mixture was combined with a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate (2 x 100 mL). Chromatography on silica (10% to 25% ethyl acetate/hexane) gave an oil which solidified on standing (7.68 g, 77%, mp 53-53 °C).

Step 2. A mixture of the product of Step 1 (200 mg, 0.77 mmol) and 0.5 M solution of 4-methylpiperidine (4 mL, 2.0 mmol) was heated at 35 °C for 60 h. The reaction mixture was combined with a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate (2 x 10 mL). The extracts were dried and evaporated to dryness. The crude product was filtered though a short silica column and treated with a 1.0 M solution of hydrogen chloride gas in ether. The solid was filtered and dried to give the hydrochloride salt (220 mg, 80 %): MS(ES) 323 (M+H).

By following the procedures of Example 2, but replacing 4-methylpiperidine in Step 2 with the appropriate amine, the following compounds were prepared. The ^{1}H NMR spectrum and the mass spectrum for each of these compounds were consistent with the assigned structure.

1. 3-[4-(3-Chlorophenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;
2. 3-(3-Methylpiperidin-1-yl)propylsulfonyl-2,3-dihydro-1*H*-indole;
3. 3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)propylsulfonyl-2,3-dihydro-1*H*-indole;
4. 3-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;
5. 3-(4-Phenylpiperazin-1-yl)propylsulfonyl-2,3-dihydro-1*H*-indole;
6. 3-[4-(2-Fluorophenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;
7. 3-[4-(2-Methoxyphenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;
8. 3-[4-(4-Methoxyphenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;
9. 3-[4-(2-Chlorophenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole.

By following the procedures of Example 2, but replacing the indoline in Step 1 with *N*-methylaniline and the 4-methylpiperidine in Step 2 with the appropriate amine, the following compounds were prepared. The ^{1}H NMR spectrum and the mass spectrum for each of these compounds were consistent with the assigned structure.

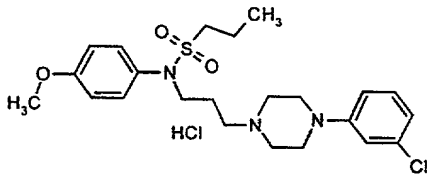
10. 3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)-*N*-methyl-*N*-phenyl-propylsulfonamide;
11. *N*-Methyl-*N*-phenyl-3-[4-(3-trifluoromethylphenyl)piperazin-1-yl]propylsulfonamide;
12. *N*-Methyl-*N*-phenyl-3-(4-phenylpiperazin-1-yl)propylsulfonamide;
13. 3-[4-(2-Fluorophenyl)piperazin-1-yl]- *N*-methyl-*N*-phenyl-propylsulfonamide;
14. *N*-Methyl-3-[4-(2-methoxyphenyl)piperazin-1-yl]-*N*-phenyl-propylsulfonamide;
15. 3-[4-(2-Chlorophenyl)piperazin-1-yl]- *N*-methyl-*N*-phenyl-propylsulfonamide

By following the procedures of Example 2, but replacing the 3-chloropropanesulfonyl chloride in Step 1 with 2-chloroethanesulfonyl chloride and the 4-methylpiperidine in Step 2 with 3-methylpiperidine, the following compound was prepared. The ^{1}H NMR spectrum and the mass spectrum for this compound were consistent with the assigned structure.

16. 2-(3-Methylpiperidin-1-yl)ethylsulfonyl-2,3-dihydro-1*H*-indole.

Example 3

N-[3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide Hydrochloride



Step 1. To a solution of *p*-anisidine (6.00 g, 48.7 mmol) and triethylamine (5.91 g, 58.4 mmol) in methylene chloride (200 mL) at 0°C was added propylsulfonyl chloride (7.64 g, 53.6 mmol) with stirring under nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was washed with a saturated aqueous solution of sodium bicarbonate (100 mL), water, and dried over magnesium sulfate. The organic layer was evaporated to give an oil that was mixed with a solution of hexane and ethyl acetate (3:1) to afford a crystalline solid (7.97 g). The mother liquid was chromatographed on silica (hexane/ethyl acetate, 4:1) to give a solid (2.27 g, 92%): mp 72°C; MS(-ES) 228 (M-H).

Step 2. To the product of Step 1 (3.50 g, 15.3 mmol) in anhydrous dimethylformamide (80 mL) at 0°C was added sodium hydride (60 % suspension in mineral oil, 0.672 g, 16.8 mmol) under a nitrogen atmosphere. The suspension was stirred for 30 min and 1,3-dibromopropane (9.27 g, 45.9 mmol) was added over 1 min. The reaction was stirred for 3 h, mixed with a saturated aqueous solution of sodium bicarbonate (200 mL) and extracted with ethyl acetate (3 x 100 mL). The combined extracts were dried and evaporated to dryness. Chromatography on silica (20% ethyl acetate in hexane) gave a colorless oil (4.33 g, 81%): MS(+ES) 352 (M+H).

Step 3. To a solution of the product of Step 2 (0.175 g, 0.50 mmol) in anhydrous dimethylformamide (1 mL) was added a 0.5 M solution of 1-(3-chlorophenyl)piperazine in dimethylformamide (1.1 mL, 0.55 mmol) and triethylamine (0.20 mL); this mixture was heated at 60°C for 18 h. The cooled reaction mixture was extracted with ethyl acetate (2 x 1 mL) and the combined extracts were washed with a saturated aqueous solution of sodium

bicarbonate, dried and evaporated to an oil which was treated with a 1.0 M solution of hydrogen chloride gas in ether to give the corresponding salt (0.11 g, 44%): MS(ES) 466 (M+).

By following the procedures of Example 3, but replacing 1-(3-chlorophenyl)piperazine in Step 3 with the appropriate amine, the following compounds were prepared. The ^{1}H NMR spectrum and the mass spectrum for each of these compounds were consistent with the assigned structure.

1. *N*-[3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
2. *N*-[3-(3-Hydroxymethylpiperidin-1-yl)propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
3. *N*-(4-Methoxyphenyl)-*N*-[3-(morpholin-4-yl)propyl]-propanesulfonamide;
4. *N*-(4-Methoxyphenyl)-*N*-[3-(2-methylpiperidin-1-yl)propyl]-propanesulfonamide;
5. *N*-[3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
6. *N*-(4-Methoxyphenyl)-*N*-[3-[4-(3-trifluoromethylphenyl)piperazin-1-yl]propyl]-propanesulfonamide;
7. *N*-[3-(4-phenylpiperazin-1-yl)propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
8. *N*-[3-[4-(2-Fluorophenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
9. *N*-[3-[4-(4-Methoxyphenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
10. *N*-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
11. *N*-[3-[4-(2-Chlorophenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;
12. *N*-[3-[4-(2*H*-Benzimidazo-2-oxo-1-yl)piperidin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide.

By following the procedures of Example 3, but replacing the 1,3-dibromopropane in Step 2 with 1,4-dibromobutane and the 1-(3-chlorophenyl)piperazine in Step 3 with 1,2,3,4-

tetrahydroisoquinoline, the following compound was prepared. The ^{1}H NMR spectrum and the mass spectrum for this compound were consistent with the assigned structure.

13. *N*-[4-(1,2,3,4-Tetrahydroisoquinolin-2-yl)butyl]-*N*-(4-methoxyphenyl)-methanesulfonamide.

The following topical ophthalmic formulations are useful according to the present invention administered 1-4 times per day according to the discretion of a skilled clinician.

EXAMPLE 4

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
Hydroxypropyl methylcellulose	0.5%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 5

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
Hydroxypropyl methylcellulose	0.5%
Cremophor EL	0.1%
Tromethamine, USP, AR	0.64%
Mannitol, USP	3.0%
Boric acid, USP	0.3%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 6

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
Methyl cellulose	4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 7

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
Hydroxypropyl-β-cyclodextrin	4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 8

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
Xanthan gum	0.5-6.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 9

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
Guar gum	0.4- 6.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 10

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
Tyloxapol	0.2 – 4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

EXAMPLE 11

Ingredients	Amount (wt %)
$5HT_7$ Compound	0.01 – 2%
White petrolatum and mineral oil and lanolin	Ointment consistency
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4

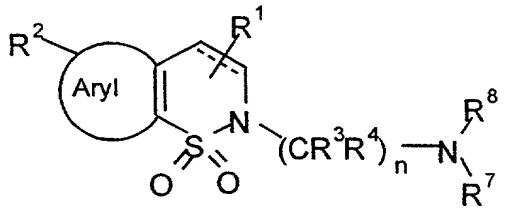
EXAMPLE 12

Formulation for Oral Administration

Tablet: 0.2 - 5 mg. of $5HT_7$ Compound with inactive ingredients such as cornstarch, lactose, colloidal silicon dioxide, microcrystalline cellulose, and magnesium sterate can be formulated according to procedures known to those skilled in the art of tablet formulation.

We Claim:

1. A compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

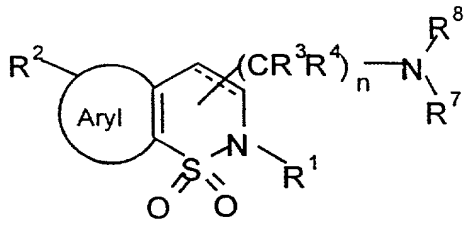
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

2. A compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted

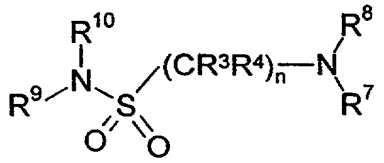
optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

3. A compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

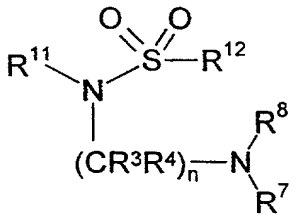
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

4. A Compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

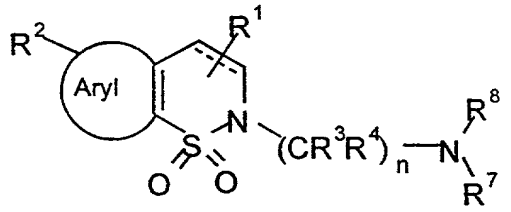
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

5. A method for lowering IOP which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

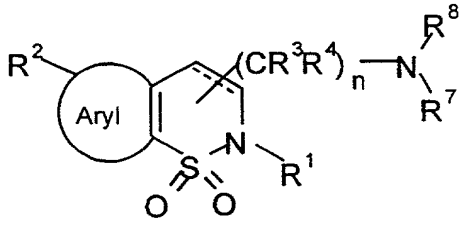
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

6. A method for lowering IOP which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or

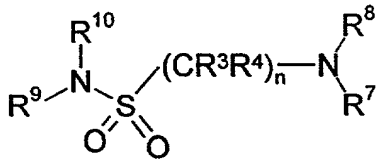
more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

7. A method for lowering IOP which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

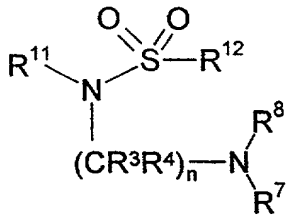
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

8. A method for lowering IOP which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

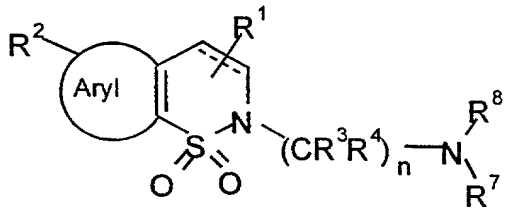
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

9. A method for improving blood flow to the optic nerve head and the retina which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

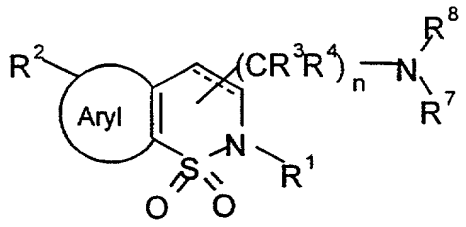
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

10. A method for improving blood flow to the optic nerve head and the retina which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine

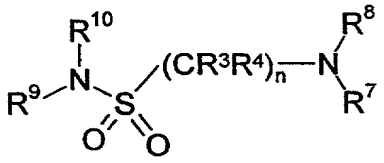
or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

11. A method for improving blood flow to the optic nerve head and the retina which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

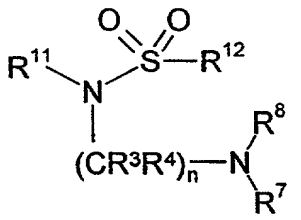
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

12. A method for improving blood flow to the optic nerve head and the retina which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

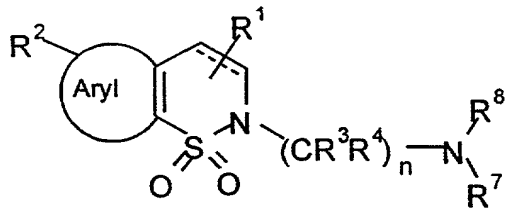
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

13. A method for treating retinal diseases which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

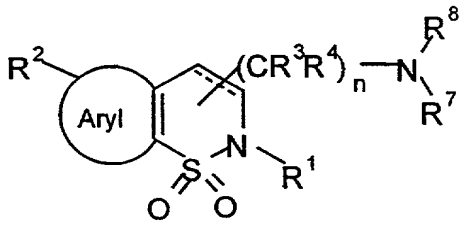
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

14. A method for treating retinal diseases which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2NR^5R^6$; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2NR^5R^6$; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected

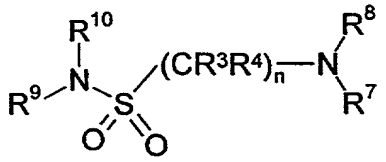
from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

15. A method for treating retinal diseases which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

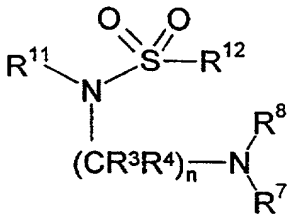
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

16. A method for treating retinal diseases which comprises administering to a person in need thereof, a composition comprising an effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

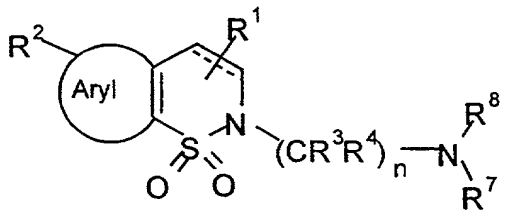
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

17. A composition for lowering IOP comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

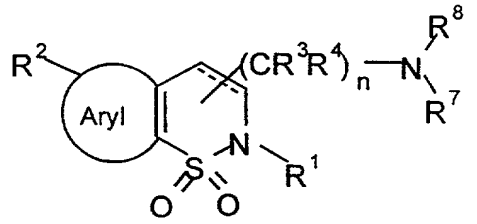
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

18. A composition for lowering IOP comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or

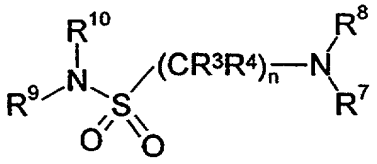
more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

19. A composition for lowering IOP comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

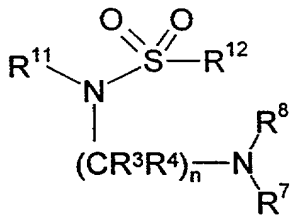
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

20. A composition for lowering IOP comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

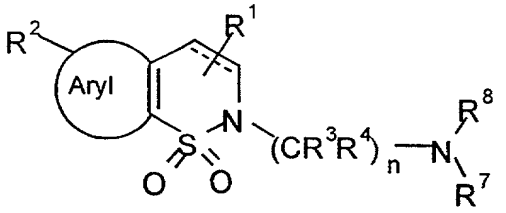
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

21. A composition for improving blood flow to the optic nerve head and the retina comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

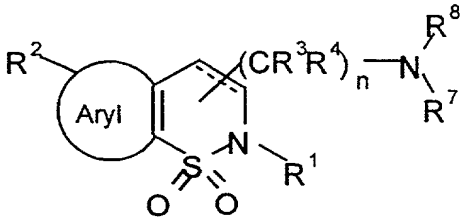
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

22. A composition for improving blood flow to the optic nerve head and the retina comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen

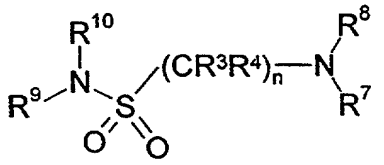
with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

23. A composition for improving blood flow to the optic nerve head and the retina comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

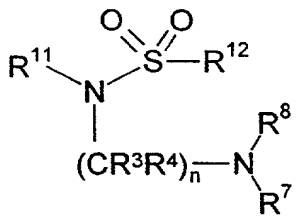
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

24. A composition for improving blood flow to the optic nerve head and the retina comprising a pharmaceutically effective amount of a Compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

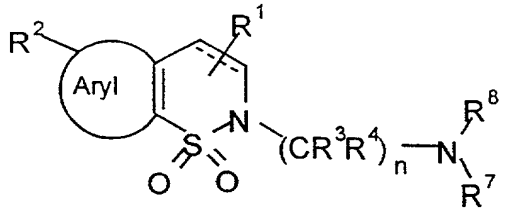
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

25. A composition for treating retinal diseases comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

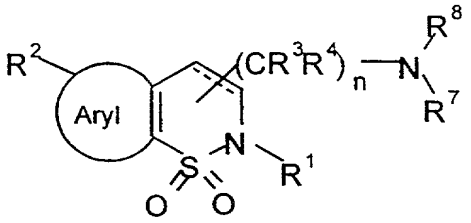
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

26. A composition for treating retinal diseases comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen

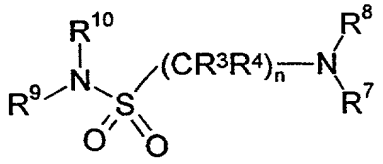
with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

27. A composition for treating retinal diseases comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

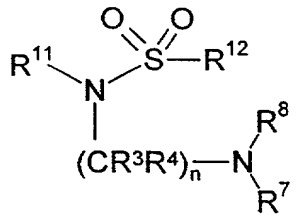
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

28. A composition for treating retinal diseases comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

29. A method for improving blood flow to the optic nerve head or the retina which comprises administering to a person in need thereof, a composition comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

30. A composition for improving blood flow to the optic nerve head or the retina comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

31. A method for providing neuroprotection to the optic nerve head or the retina which comprises administering to a person in need thereof, a composition comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

32. A composition for providing neuroprotection to the optic nerve head or the retina comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

33. A method for treating retinal diseases which comprises administering to a person in need thereof, a composition comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

34. The method of Claim 1 wherein the retinal disease is selected from the group consisting of glaucoma, age related macular degeneration, optic neuritis, ischemic disorders, and retinal edema.

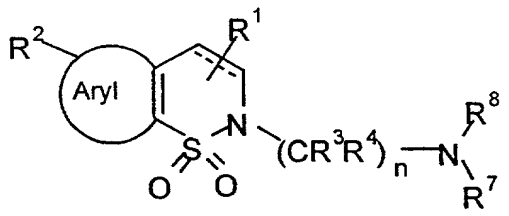
35. A composition for treating retinal diseases comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

36. The composition of Claim 35 wherein the retinal diseases are selected from the group consisting of glaucoma, age related macular degeneration, optic neuritis, ischemic disorders, diabetic retinopathy, and retinal edema.

37. A method for lowering IOP which comprises administering to a person in need thereof, a composition comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

38. A composition for lowering IOP comprising a pharmaceutically effective amount of a compound with $5HT_7$ receptor affinity.

39. A method for treating persons suffering from a sleeping disorder, depression, schizophrenia, anxiety, circadian rhythm disorders, and centrally and peripherally mediated hypertension, which comprises, administering a composition comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

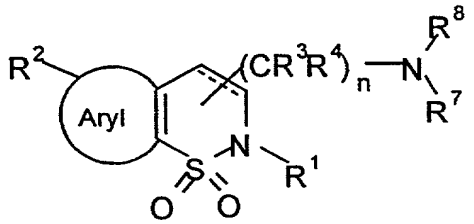
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

40. A method for treating persons suffering from a sleeping disorder, depression, schizophrenia, anxiety, obsessive compulsive disorder, circadian rhythem disorders, and centrally and peripherally mediated hypertension which comprises, administering a composition comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2$ NR^5R^6; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2$ NR^5R^6; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2$ NR^5R^6, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

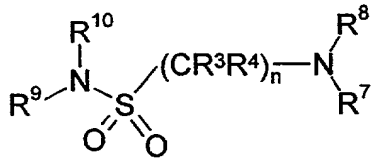
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates.

41. A method for treating persons suffering from a sleeping disorder, depression, schizophrenia, anxiety, obsessive compulsive disorders, circadian rhythm disorders, and centrally and peripherally mediated hypertension which comprises, administering a composition comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen

with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

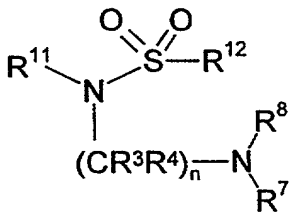
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

42. A method for treating persons suffering from a sleeping disorder, depression, schizophrenia, anxiety, obsessive compulsive disorder, circadian rhythm disorders, and centrally and peripherally mediated hypertension which comprises, administering a composition comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

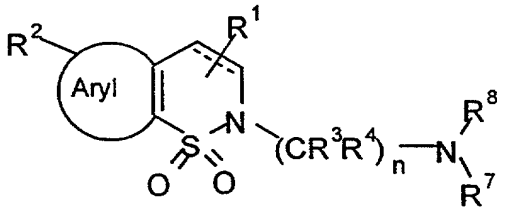
R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates.

43. A composition comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, OH, OC_{1-3}alkyl, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $CONR^5R^6$, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3, R^4 are independently H, C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6 membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted

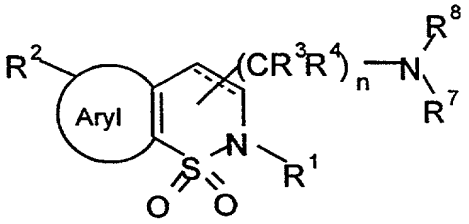
optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates in a pharmaceutically acceptable carrier.

44. A composition comprising a pharmaceutically effective amount of a compound of the formula:



Wherein the dashed bond represents a single or double bond;

Aryl signifies a fused phenyl or monocyclic heteroaromatic ring;

R^1 is H, C_{1-5}alkyl, C_{3-5}alkenyl, an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, or $S(=O)_2NR^5R^6$; or C_{2-5}alkyl substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl or an aromatic ring such as phenyl, thienyl, pyridyl, and imidazoyl which is either unsubstituted or substituted optionally with OH, OC_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, halogen, CF_3, $S(=O)_2NR^5R^6$; or C_{3-5}alkenyl substituted optionally with OH, OC_{1-3}alkyl, or $S(=O)_mC_{1-3}$alkyl;

R^2 is H, halogen, C_{1-3}alkyl, $S(=O)_mC_{1-3}$alkyl, $S(=O)_2NR^5R^6$, or C_{1-3}alkyl substituted optionally with OH, or OC_{1-3}alkyl;

R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^5, R^6 are independently H, C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, or R^5 and R^6 can be joined together with saturated carbon atoms to form a 5 or 6

membered ring and said carbon atoms can be either unsubstituted or substituted optionally with C_{1-3}alkyl, C_{2-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

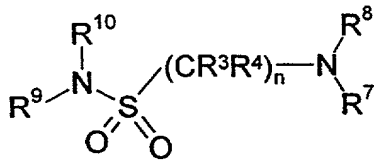
R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

n is 2 to 4;

m is 0, 1 or 2

and any pharmaceutically acceptable salts and solvates in a pharmaceutically acceptable carrier.

45. A composition comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen

with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

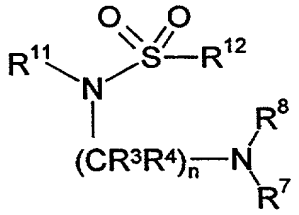
R^9 is phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{10} is C_{1-4}alkyl, or R^{10} can be joined to R^9 to form a fused bicyclic ring system such as indoline;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates in a pharmaceutically acceptable carrier.

46. A composition comprising a pharmaceutically effective amount of a compound of the formula:



R^3 & R^4 are independently H, C_{1-3}alkyl, or C_{1-3}alkyl substituted optionally with OH or OC_{1-3}alkyl;

R^7, R^8 are together with the nitrogen atom to which they are attached incorporated into a heterocyclic ring of 5 to 8 atoms which may include a second heteroatom selected from N, O, S, such as pyrrolidine, piperidine, Δ^3-piperidein, piperazine, morpholine or thiomorpholine which can be unsubstituted or substituted on carbon with one or more substituents optionally selected from C_{1-3}alkyl, C_{1-3}alkyl substituted optionally with OH, OC_{1-3}alkyl, phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl, or substituted on nitrogen with C_{1-4}alkoxy or phenyl which can be unsubstituted or substituted optionally with halogen, CF_3, OC_{1-3}alkyl, or C_{1-3}alkyl;

R^{11} is C_{1-3}alkyl, phenyl or a monocyclic heteroaromatic ring which can be unsubstituted or substituted with C_{1-4} alkyl, halogen, OC_{1-4}alkyl;

R^{12} is C_{1-4}alkyl or a fused bicyclic heteroaromatic ring such as thieno[3,2-*e*]-1,2-thiazine, or 1,2-benzothiazine, or R^{12} can be joined to R^{11} to form a fused bicyclic ring system such as 2,3-dihydro-benzo[*c*]isoxazole;

n is 2 to 4

and any pharmaceutically acceptable salts and solvates in a pharmaceutically acceptable carrier.

47. The Compound of Claim 1 selected from the group consisting of:

6-Chloro-2-[4-[4-(2*H*-benzimidazo-2-oxo-1-yl)piperidin-1-yl]butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide;

6-Chloro-2-[4-(4-phenylpiperazin-1-yl)butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide;

6-Chloro-2-[4-[4-(2-fluorophenyl)piperazin-1-yl]butyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide;

6-Chloro-2-[3-[4-(3-trifluoromethylphenyl)piperazin-1-yl]propyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide;

6-Chloro-2-[3-[4-(2*H*-benzimidazol-2-oxo)piperidin-1-yl]propyl]-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide.

48. The Compound of Claim 3 selected from the group consisting of:

3-[4-(3-Chlorophenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;

3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)propylsulfonyl-2,3-dihydro-1*H*-indole;

3-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;

3-[4-(2-Methoxyphenyl)piperazin-1-yl]propylsulfonyl-2,3-dihydro-1*H*-indole;

3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)-*N*-methyl-*N*-phenyl-propylsulfonamide;

49. The Compound of Claim 4 selected from the group consisting of:

N-[3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;

N-[3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;

N-[3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;

N-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide;

N-[3-[4-(2-Chlorophenyl)piperazin-1-yl]propyl]-*N*-(4-methoxyphenyl)-propanesulfonamide.

Express Mail No. EK810444575US

Please type a plus sign (+) inside this box → [+]

PTO/SB/01 (12-97)
Approved for use through 9/30/00. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☑ Declaration Submitted with Initial Filing **OR** ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	1700F US
First Named Inventor	May
COMPLETE IF KNOWN	
Application Number	/ NYA
Filing Date	31.10.00 (31 October 2000)
Group Art Unit	NYA
Examiner Name	NYA

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

SEROTONERGIC 5HT7 RECEPTOR COMPOUNDS FOR TREATING OCULAR AND CNS DISORDERS

(Title of the Invention)

the specification of which
☐ is attached hereto
OR
☑ was filed on (MM/DD/YYYY) 05.10.99 (May 10, 1999) ✓ as United States Application Number or PCT International Application Number PCT/US99/10179 ✓ and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)
60/086,006 ✓	May 19, 1998 ✓
60/086,005 ✓	May 19, 1998 ✓
60/086,002 ✓	May 19, 1998 ✓
60/085,989 ✓	May 19, 1998 ✓

☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

Burden Hour Statement: This form is estimated to take 0.4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

Please type a plus sign (+) inside this box → [+]

PTO/SB/01 (12-97)
Approved for use through 9/30/00. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION — Utility or Design Patent Application

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*
PCT/US99/10179	05.10.99 May 10, 1999	

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: ☐ Customer Number [ ] → *Place Customer Number Bar Code Label here*
OR
☑ Registered practitioner(s) name/registration number listed below

Name	Registration Number	Name	Registration Number
ARNO, James A.	26,145	SHIRA, Jeffrey S.	34,922
BROWN, Gregg C.	30,613	RYAN, Patrick M.	36,263
YEAGER, Sally	32,757	LEE, W. David	39,743
COPELAND, Barry	34,801		

☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto.

Direct all correspondence to: ☑ Customer Number or Bar Code Label [barcode] *OR* ☐ Correspondence address below

26356
PATENT TRADEMARK OFFICE

Name					
Address					
Address					
City		State		ZIP	
Country		Telephone		Fax	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Jesse A.	May

Inventor's Signature	Jesse A. May					Date	10/30/00
Residence: City	Fort Worth	State	TX	Country	US	Citizenship	US
Post Office Address	4132 Hildring Drive East						
Post Office Address							
City	Fort Worth	State	TX	ZIP	76109	Country	US

☑ Additional inventors are being named on the 1 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

Express Mail No.EK810444575US

Please type a plus sign (+) inside this box → [+]

PTO/SB/02A (3-97)
Approved for use through 9/30/98. OMB 0651-0032
Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 1

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Thomas R.	Dean

2-00

Inventor's Signature	Thomas R. Dean					Date	10/30/00
Residence: City	Weatherford TX	State	Tx	Country	US	Citizenship	US
Post Office Address	101 Meadow View Court						
Post Office Address							
City	Weatherford	State	Tx	ZIP	76087	Country	US

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Najam A.	Sharif

3-00

Inventor's Signature	Najam Sharif					Date	10/31/00
Residence: City	Arlington TX	State	TX	Country	US	Citizenship	UK
Post Office Address	7 Courtney Court						
Post Office Address							
City	Arlington	State	TX	ZIP	76015	Country	US

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Hwang-Hsing	Chen

4-00

Inventor's Signature	H Chen					Date	10/30/00
Residence: City	Fort Worth TX	State	TX	Country	US	Citizenship	US
Post Office Address	7649 Grassland Drive						
Post Office Address							
City	Fort Worth	State	TX	ZIP	76133	Country	US

Burden Hour Statement: This form is estimated to take 0.4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

[+]